CLAIMS

What is claimed is:

1. A gene-targeted non-human animal comprising a modified endogenous apolipoprotein E (apoE) allele, wherein said modified allele comprises an apoE-encoding nucleic acid under transcriptional control of endogenous regulatory sequences, and wherein the modified allele encodes a modified apoE that exhibits domain interaction characteristic of human apolipoprotein E4 (apoE4).

2. The non-human animal of claim 1, wherein the modified apoE comprises a Thr → Arg substitution at a position equivalent to amino acid 61 of human apoE4.

3. The non-human animal of claim 1, wherein the gene-targeted non-human animal is homozygous for the modified apoE allele.

4. The non-human animal of claim 1, wherein the gene-targeted animal is a mouse.

5. An isolated non-human cell comprising a modified endogenous apolipoprotein E (apoE) allele, wherein said modified endogenous allele is under transcriptional control of endogenous regulatory sequences, and wherein the modified allele encodes a modified apoE that exhibits domain interaction characteristic of human apolipoprotein E4 (apoE4).

6. The non-human cell of claim 5, wherein the modified apoE comprises a Thr → Arg substitution at a position equivalent to amino acid 61 of human apoE4.

7. The non-human cell of claim 5, wherein the cell is homozygous for the modified apoE allele.

8. The non-human cell of claim 5, wherein the cell is a mouse cell.

9. An isolated nucleic acid molecule comprising a nucleotide sequence derived from a non-human apolipoprotein E (apoE) gene, which nucleotide sequence is modified such that it encodes a protein comprising a Thr → Arg substitution at a position equivalent to amino acid 61 of human apoE4.

10. A recombinant vector comprising the nucleic acid of claim 9.

11. A recombinant host cell comprising the vector of claim 10.

12. A recombinant apolipoprotein E (apoE) protein encoded by a nucleic acid comprising a nucleotide sequence derived from a non-human apoE gene, which nucleotide sequence is modified such that it encodes a protein that exhibits domain interaction characteristic of human apolipoprotein E4 (apoE4).

13. The recombinant protein of claim 12, wherein the recombinant protein comprises a Thr → Arg substitution at a position equivalent to amino acid 61 of human apoE4.

14. A method of identifying an agent that reduces a phenomenon associated with Alzheimer's disease (AD), the method comprising:

a) contacting the gene-targeted non-human animal of claim 1 with a test agent; and

b) determining the effect of the test agent on a phenomenon associated with AD.

15. The method of claim 15, wherein the phenomenon associated with AD is selected from the group consisting of amyloid deposits, neuronal cell loss, and neurofibrillary tangles.

16. A method for identifying an agent that reduces apolipoprotein E4 domain interaction, the method comprising:

a) contacting the recombinant protein of claim 12 with a test agent; and

b) determining the effect of the test agent on domain interaction.

17. The method of claim 16, wherein said determining comprises determining binding of the recombinant apoE to tau.

18. The method of claim 16, wherein said determining comprises determining the effect of the agent on binding to VLDL.

19. A method of identifying an agent that reduces the risk of heart disease, comprising:

a) contacting the non-human animal of claim 1 with a test agent; and

b) determining the effect, if any, on apoE activity.